THE EFFECTIVENESS OF THE ORAL VITAMIN B6 ON THE BEHAVIORAL SIDE EFFECTS OF PHENOBARBITAL IN CHILDREN 2 TO 15 YEARS OLD WITH SEIZURES

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ABSTRACT

Objectives*: Behavioral problems are considered as the side effects of phenobarbital consumption in children. Thus, the aim of this research is studying the effect of vitamin B6 on behavioral disorders due to use of phenobarbital in patients with seizure.*

Patients and methods*: In this study, 77 patients (Children with Seizures) were studied and divided to needs to be removed two groups. Phenobarbital along with vitamin B6, and phenobarbital along with a placebo were separately prescribed to the two groups for three months, and behavioral changes were recorded and the data were collected and provided for the statistical software.*

Results*: In the first three months, no significant difference was observed between the two groups, and in the second three months, the average value of hyperactivity behavior removed significantly decreased. In the drug group in the first three months and placebo group in the second three months, hyperactivity and aggressive behaviors significantly reduced moreover, With respect to all three behaviors, the placebo group in the first three months and drug group in the second three months the Were not significantly different.*

Conclusion*: vitamin B6 can be effective in the reduction of hyperactivity behavior in the children.*

Keywords*: vitamin B6, phenobarbital, behavioral disorders, seizures.*

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Introduction

Seizures is defined as the malfunction of the brain's electrical system originated from the evacuation of cerebral cortex neurons. Its signs and symptoms include lack of awareness or change in consciousness, involuntary movements, and changes in perceptions, behaviors, and feelings[1]. Seizure is the most common treatable neurological disorder in childhood occurred by a wide range of different diseases involving the nervous system[2, 3]. Seizure with prevalence of 4 to 6 cases in 1000 children, are considered as the most common neurological disorder in pediatrics[4]. Five million people worldwide suffer from epilepsy in which 3 million of them are children and 90% of these children live in developing countries[5].

Phenobarbital is one of the oldest, safest, and least expensive used drugs in the treatment of seizure disorders[6]. This drug has been introduced by the WHO as first-line treatment for generalized tonic-clonic and partial seizures in developing countries[7, 8]. However, the use of phenobarbital for febrile seizures in children due to reported behavioral problems is under discussion and its consumption in developed countries regarding newer drugs with fewer effects on behavioral functions is declining[9]. Also, when other drugs are contraindicated due to serious hematologic or hepatic side effects, phenobarbital can be a first-line treatment especial-

ly when drug price is a primary concern[8, 10]. Behavioral problems mentioned as side effects of phenobarbital include hyperactivity, aggressive behavior, inattention, and restlessness[11]. Sylvia et al. (1995) indicated that 60% of children, receiving phenobarbital to treat febrile seizure, suffer from behavioral problems that led to The discontinuation of treatment[12]. The incidence of behavioral problems in children with epilepsy is two times higher than children with chronic disease that does not involve the central nervous system and it is four times more than healthy children[13-16]. Behavioral problems in 20 to 50% of children with febrile seizure, receiving phenobarbital, have been reported and led to be discontinuation of treatment in 20 to 30% of them[11]. Also, the prevalence of behavioral disorders originated from phenobarbital in patients with mental retardation and developmental disorders is considerably high[17].

many studies have been done on the effect of vitamin B6 in behavioral disorders in autistic patients, panic attacks, and ADHD and etc. and Its positive effects on behavioral disorders have been reported given the use of levetiracetam in children with elipsy[18-21], this study work aims to investigate the effect of vitamin B6 on behavioral disorders due to use of phenobarbital in epileptic patients ages 2 to 15 years treated with this drug.

Materials and methods

This Study is a double-blind randomized One. The Statistical society includes all patients with seizures between 2 and 15 years of PHE consumption In this study77 people were enrolled and divided into two intervention groups with drug (41 patients) and placebo (n = 36). The available sampling method was used in this study. The method reported by Kelsey and et al.[22] has been applied to obtain a sample size of each group. Required data was collected through the Conner's parent rating scale questionnaire[23] that has the high validity and has been regarded A standard test. Conners and et al. have reported the reliability and validity of this scale Is equal to to 0.9. Additionally, and the validity of this questionnaire have been reported As to 0.85 by the Institute of Cognitive Science[24]. Here, 8 cases of Conners questionnaire have been considered in which 3, 3, and 2 cases are in relation to Hyperactivity behavior, aggression, and attention deficit, respectively. Patients' followup was done through phone calls and resourcing patients accompany with parents to the medical center. Patients have had no history of Anticonvulsants (phenobarbital) consumption. Patients 2 to 15 years old with seizure disorders were randomly assigned to two groups receiving drug (B6) and placebo. Factors such as gender, family history, history of drug etc. Have not been included in the study. The excluded factors included background psychological disorders (SADS-KIDS), background disease, and disinclination to enter the study.

In the first three months of study, a drug was given to a group and a placebo to the other group. After 10 days of washed out, the place of the two groups were replaced and then the treatment was carried out for three months, again. At the end of each study, the data was collected by filling out a questionnaire and data analysis was performed using SPSS software. To test the hypothesis, T-test and Chi- square statistical methods were used.

Phenobarbital: Phenobarbital is one of the sedative drugs has been widely used for the treatment of various forms of epilepsy, especially in children. There are tablets 15, 60 and 100 mg, and vials 100 and 200 mL of Phenobarbital. The onset of this drug varies from 10 minutes (IV administration) to 60 minutes (oral administration), and duration of drug action varies from 4 hours to less than 6 hours. Its half-life is generally 50 - 140 hours [6, 25].

Vitamin B6: Vitamin B6 is one of the water soluble vitamins that plays a critical role in the protein metabolism and adjusting the nervous system of the human body. This vitamin is found in the food plants and animals, but biologically, its animal sources are numerous. There are tablet 40 mg, and vials 50, 100 and 150 mL of B6 vitamin, and its half-life is generally 15 - 20 days. Vitamin B6 used in the present study contains a dose 100 - 150 mg, and placebo purchased from Osvah Pharmaceutical Company was used [26-29].

Behavioral disorders are different groups of extremist and deviant behaviors through which the patients repeatedly violate the basic rights of others. These disorders occur in childhood or adolescence, and are more common in boys regarding to girls. Behavioral problems originated from phenobarbital consumption include hyperactivity, aggressive behavior, inattention and restlessness[30].

Results

The study population included two groups (placebo and control) that first group received

Phenobarbital along with vitamin B6 for three months. After 10 days, this group received placebo instead of vitamin B6 for other three months. The second group received Phenobarbital along with placebo for three months. After 10 days, this group received vitamin B6 instead of placebo for other three months.

77 patients with epilepsy were enrolled in this study. 40 patients were female and 37 were male. Also, 41 patients with a mean age of 39.19 ± 11.55 months received Phenobarbital along with vitamin B6 in first three months and 36 patients with a mean age of 37.4 ± 10.41 received Phenobarbital along with placebo in first three months. The average age of both groups was not significantly different ($p = 0.49$).

The results regarding to hyperactivity behavioral disorders, originated from the statistical analysis of data obtained from variables such as hyperactivity, Removed running or jumping in a difficult position and difficult to control in the field of in Both drug and placebo receiving groups for first three months, indicated that there was a significant difference between the two groups (p-value = 0.8).

According to results regarding to attention deficit behavioral disorders that was the sum of data obtained from variables such as "walking in class and attention deficit" and "distraction at working", no significant difference between these groups was observed for first three months. Also, the results obtained from aggressive behavior disorders, originated from the statistical analysis of data of variables such as "anger", "head banging" and "biting" showed no significant difference between the drug and placebo receiving groups.

In the second three months, the results obtained from data analysis regarding to attention deficit (p-value 0.14) and aggression (p-value 0.6) behaviors using T-test showed no significant difference between drug and placebo receiving groups. Contrarily, the difference between these groups was significant (p-value 0.01) in the field of hyperactivity behavior disorder and the average of all three indexes was higher in the placebo receiving groups.

Using Paired Sample T-Test, in the field of attention deficit behavioral disorder between drug receiving group in the first three months and placebo receiving group in the second three months was observed no significant difference (p-value 0.15). But, in regard with hyperactivity (p-value 0.001) and aggression (p-value 0.01), the difference between these groups was significant, and the average of all three indexes was higher in the placebo receiving groups.

Using Paired Sample T-Test, in the field of attention deficit (p-value 0.58), hyperactivity (p-value 0.65) and aggression (p-value 0.88) behavioral disorders between placebo receiving group in the first three months and drug receiving group in the second three months, no significant difference was observed. It's noteworthy that the average of all three indexes was higher in the placebo receiving groups.

Discussion

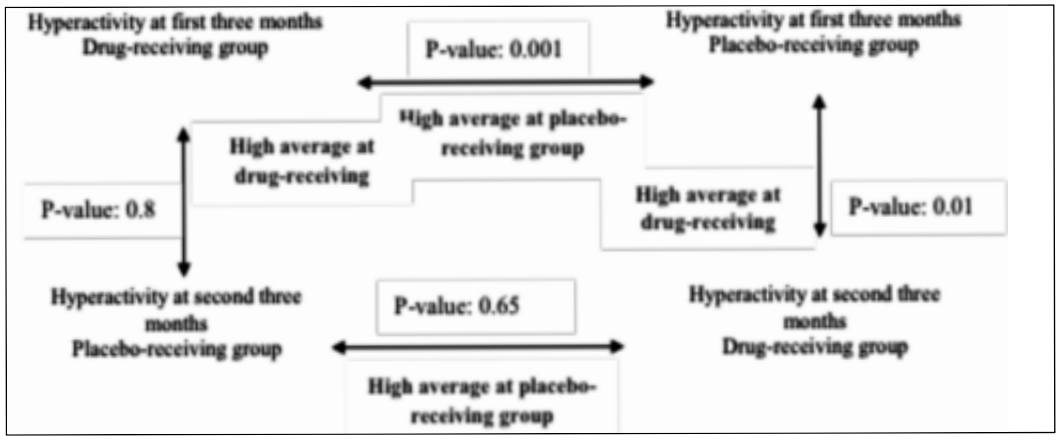
The effect of vitamin B6 consumption on the behavioral problems due to levetiracetam drug consumption has been studied by Major et al[18]. They investigated the influence of pyridoxine supplement (vitamin B6) on the behavioral side effects originated from levetiracetam consumption in the children. The behavioral side effects related to the use of levetiracetam in epilepsy are being recognized. The improvement of behavioral side effects related to the use of levetiracetam was observed after the consumption of vitamin B6.

The investigation of the behavioral problems related to the consumption of phenobarbital in the hyperactivity, attention deficit, and aggression behavioral disorders was performed by completing the questionnaire; including eight variables to evaluate each of above factors. To investigate hyperactivity behavioral disorder due to the consumption of phenobarbital, questionnaire variables include "hyperactivity", "running or jumping in a difficult position" and "difficult to control".

In the first three months of treatment, the comparison of the vitamins B6 drug receiving group and placebo receiving group showed that the average of each three variables in the drug receiving group was higher than that of placebo receiving group and the difference was not statistically significant. After 10 days of The discontinuation of vitamin B6 and the change of drug receiving group with placebo receiving group, , the average of each three variables related to hyperactivity was lower in the drug receiving group in the second three months. The difference between two groups was significant statistically.

The researchers[31] mentioned that the behavioral disorders such as hyperactivity occur by making disorder in the vitamin B6 receptors. Also, the removing substances that inhibit the absorption of

vitamin B6, improves the symptoms of hyperactivity. Contrarily, the results obtained from the investigation of hyperactivity behavior in first three months indicate that the average of hyperactivity was higher in the drug receiving group while there was no significant difference compared to the control group. However, in the second three months, the average of hyperactivity was increased in the placebo receiving group. Also, in comparison with hyperactivity behavior in the first three months, the drug receiving group showed statistically significant difference. Comparing the placebo receiving group at first three months and drug receiving group at second three months, it can be concluded that this difference may be attributed to the enhancement of symptoms resulted from the discontinuation of vitamin B6, and a positive effect of vitamin B6 on the significant decrease of the hyperactive behavior. The comparison of this study with previous studies such as levetiracetam consumption along with vitamin B6, showed that the use of vitamin B6 can strictly diminish the symptoms of hyperactivity (scheme 1).



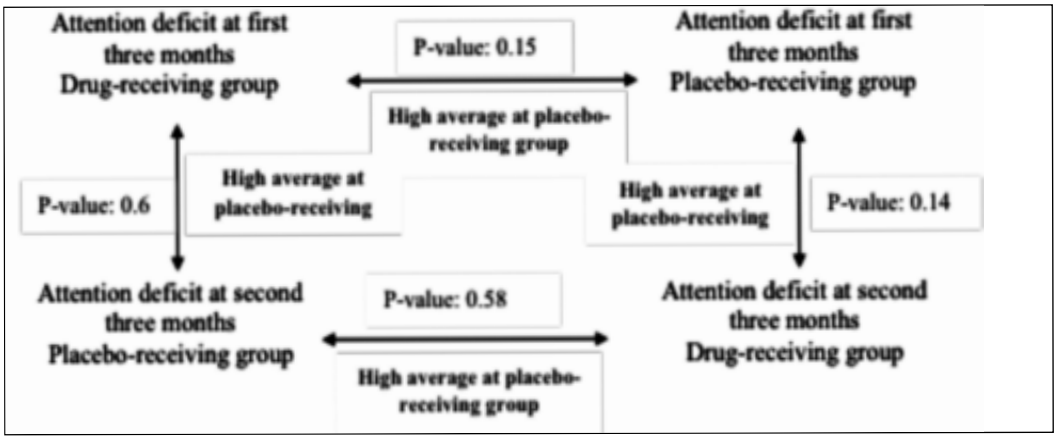
Scheme 1: The influence of phenobarbital on the hyperactivity.

Attention deficit behavior includes variables such as walking in class, attention deficit and distraction at working in the questionnaire. In the first three months, the average of each three variables in the drug-receiving group is lower than that of placebo-receiving group while the difference between two groups was not statistically significant. Also, In the second three months and after switching the drug-receiving group with placebo-receiving group, the average of each three variables is lower in the drug-receiving group while the difference between two groups was not statistically significant either. In the general investigation of attention deficit behavior due to the use of phenobarbital along vitamin B6, the average of each three variables was lower in the drug-receiving group while no significant difference was observed between these groups. It can be concluded that the vitamin B6 consumption has lower effect on the decrease of attention deficit in the children (scheme 2).

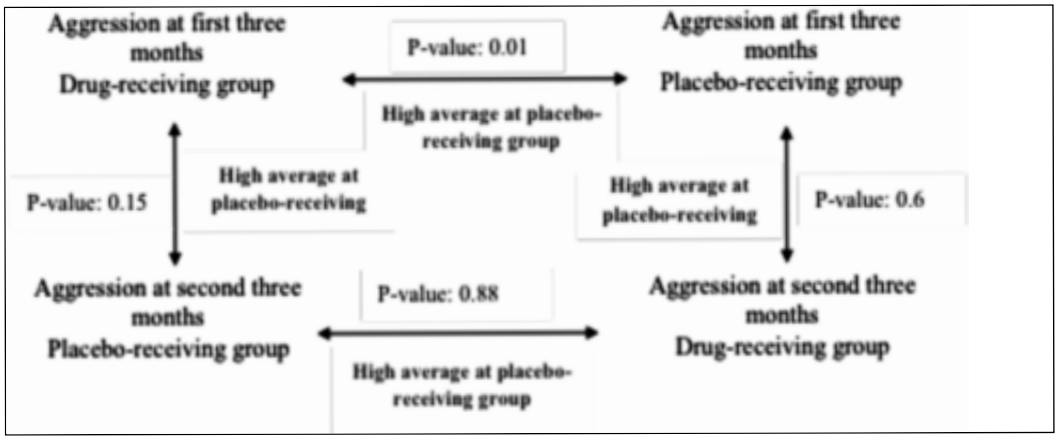
Aggressive behavior is one the side effects of the use of phenobarbital that has been Studied by variables such as madness, head slamming, and biting after treatment with the drug and placebo in the groups. It was observed that the average of each three variables in the drug-receiving group is lower than that of placebo-receiving group In the first three months. The significant difference was observed between two groups which only in the head slamming variable. At the second three months, the average of each of two variables, including madness and biting was higher in the placebo-receiving group, while the average of head banging variable was higher in the drug-receiving group, which at the second three months, this difference between any of the variables was not significant. In the general investigation of aggressive behavior at the first and second three months, average increase and significant difference were only observed in the drug-receiving group at the first three months and placebo-receiving group at the second three months. Thus, it can be said that discontinuation of vitamin B6 enhances symptoms (scheme 3).

Conclusion

The results indicated that the hyperactivity behavior was lower in the vitamin B6-receiving group, and this drug diminishes the hyperactivity



Scheme 2: The influence of phenobarbital on the Attention deficit.



Scheme 3: The influence of phenobarbital on the aggression.

behavior in the children treated with phenobarbital. Also, the enhancement of symptoms was observed owing to the discontinuation of vitamin B6. Also, it was observed that the use of vitamin B6 is not effective in reducing attention deficit behavior due to phenobarbital consumption. Finally, results confirmed that the use of vitamin B6 is not effective in reducing aggressive behavior due to phenobarbital consumption, and complete discontinuation of vitamin B6 after a course of treatment enhances this behavior in the children.

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